Acute Encephalitis Syndrome

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Outline of the presentation

- What is AES?
- History of AES in India
- Infectious causes of AES in India
- Enhanced surveillance for AES in India
- Lessons learnt from enhanced surveillance
- AFI/AES surveillance
- Non infectious causes of AES in India
- Summary

Acute Encephalitis Syndrome (AES)

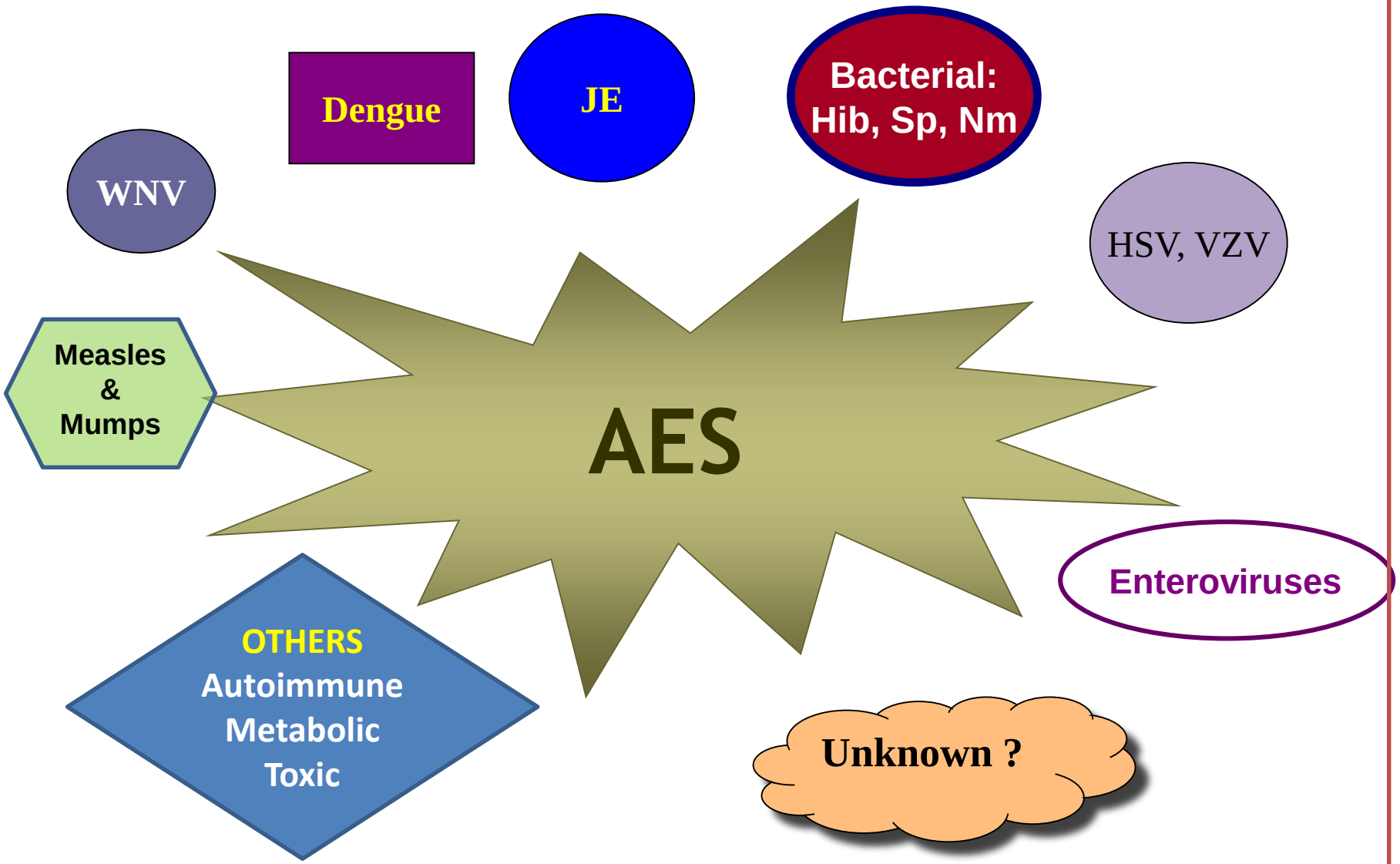
WHO Recommended case definition

- **A person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma or inability to talk)**

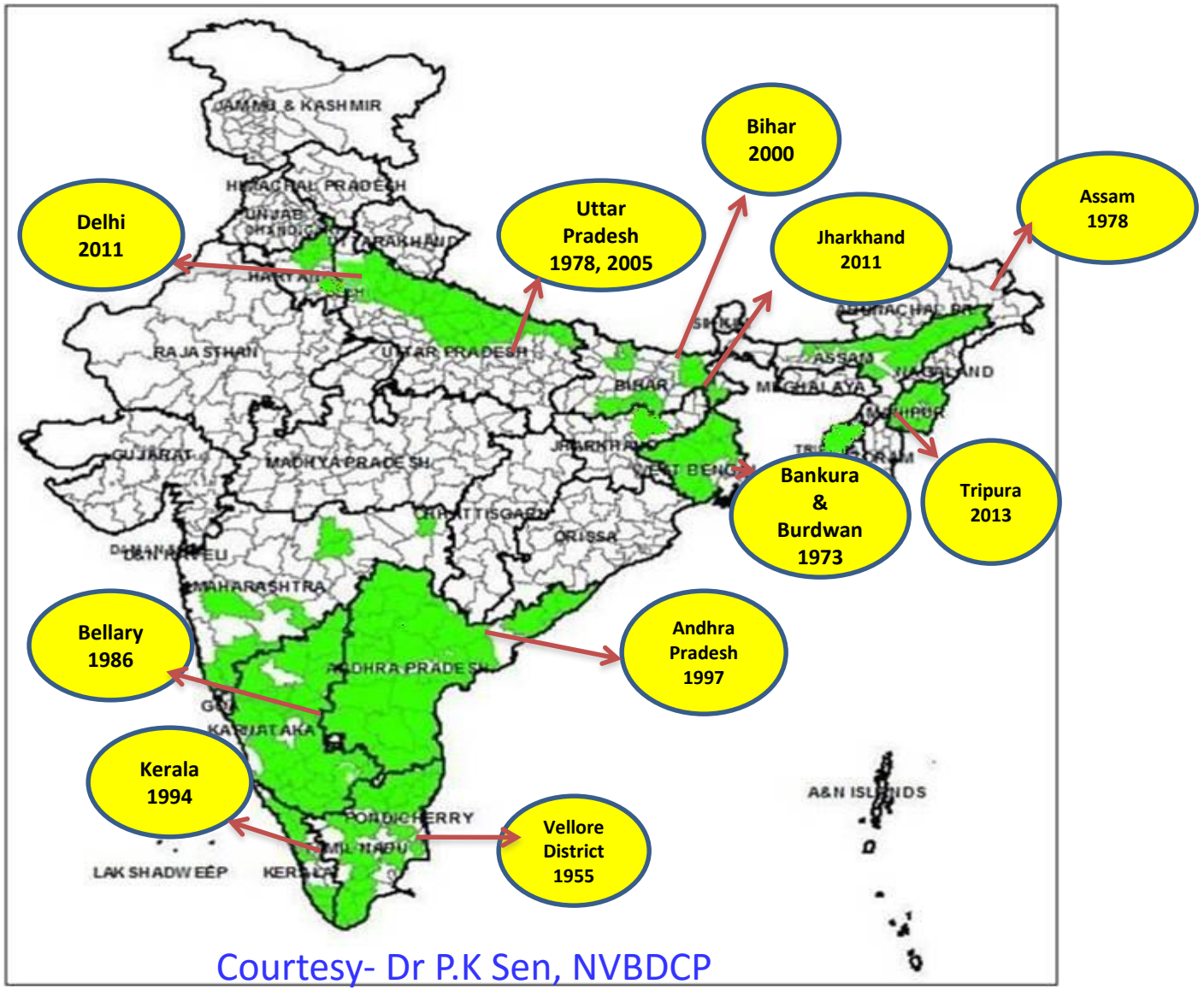
- **AND/OR new onset of seizures (excluding simple febrile seizures*).**

*** A simple febrile seizure is defined as a seizure that occurs in a child aged 6 months to less than 6 years old, whose only finding is fever and a single generalized convulsion lasting less than 15 minutes, and who recovers consciousness within 60 minutes of the seizure.**

Multiple Etiological Agents in AES

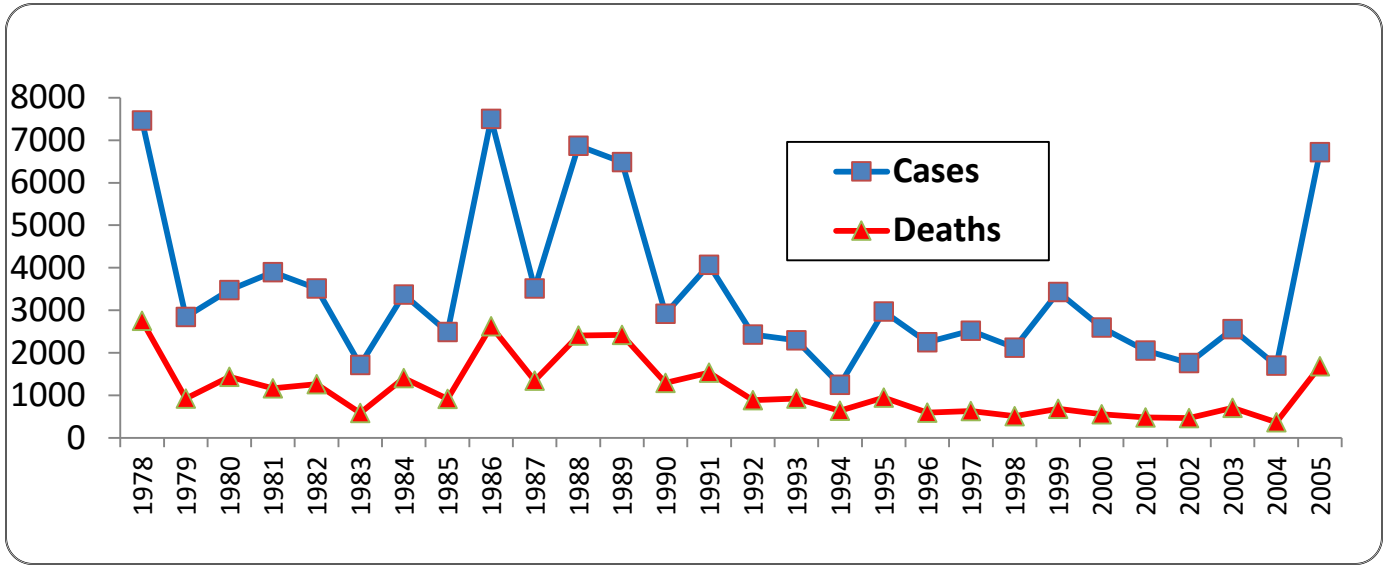


Geographic expansion of JE in India

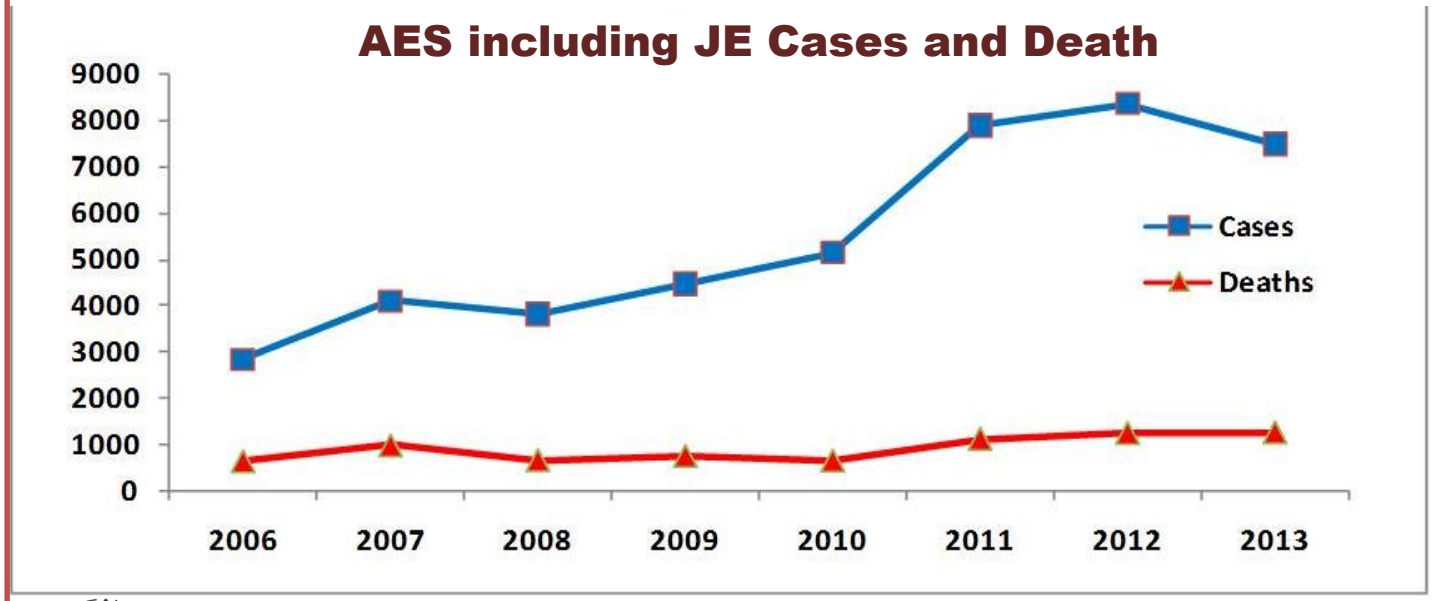


Courtesy- Dr P.K Sen, NVBDCP

Suspected JE Cases and Deaths in India



- No regular reporting system before 2005
- Routine sentinel site based surveillance after 2005



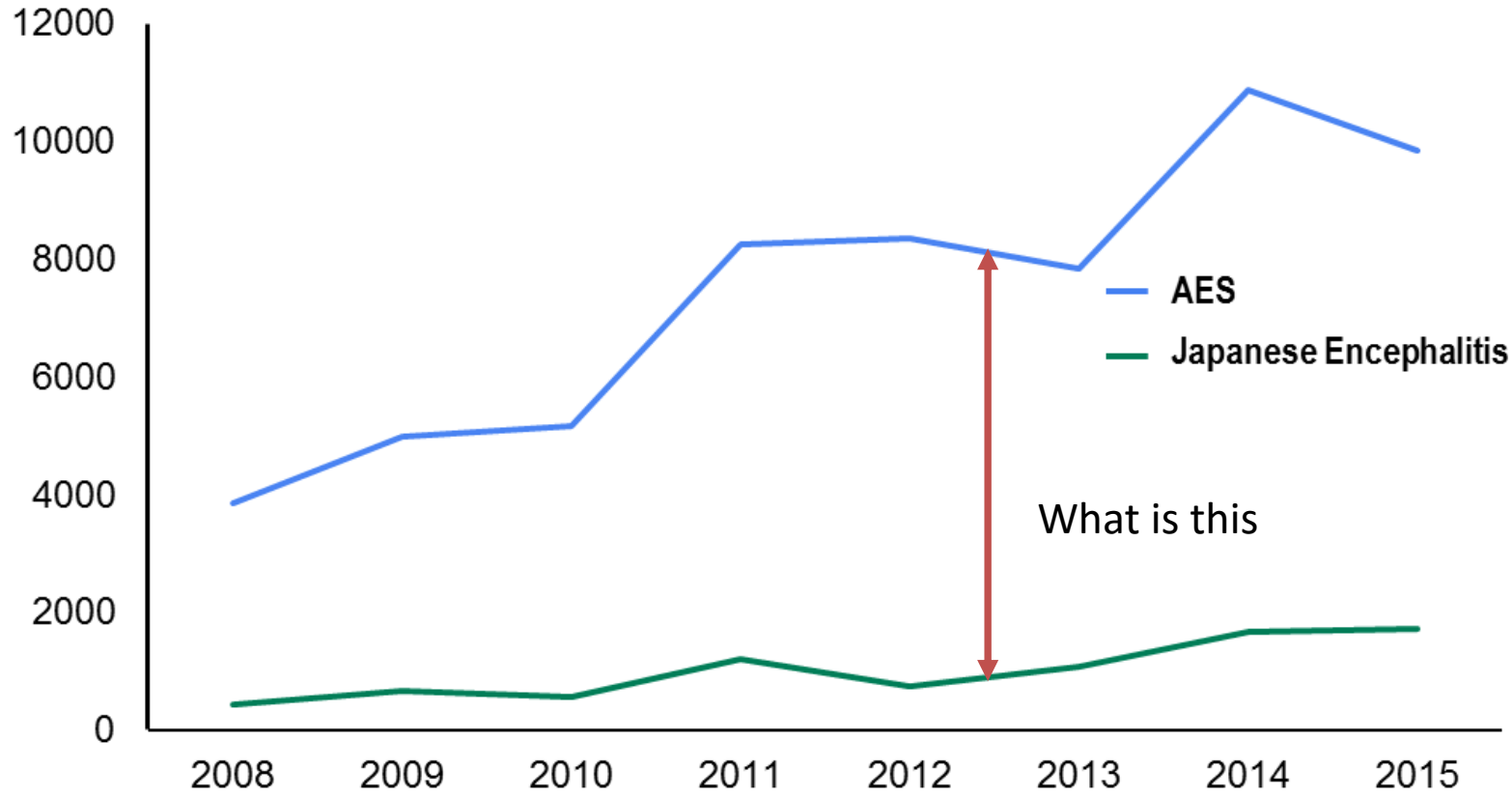
Courtesy- Dr P.K Sen, NVBDCP

Perception of AES in India : AES = JE or other viral encephalitis

- Frequent outbreaks of acute encephalitis
  - Uttar Pradesh
  - Bihar
  - West Bengal
  - Assam
  - Andhra Pradesh
  - Tamil Nadu
  - Karnataka

- Overall Etiological diagnosis is established only in 10-12% of cases

NVBDCP Surveillance Data: Reported JE/AES Cases in India, 2008 – 2015



Source: NVBDCP

AES: Challenges

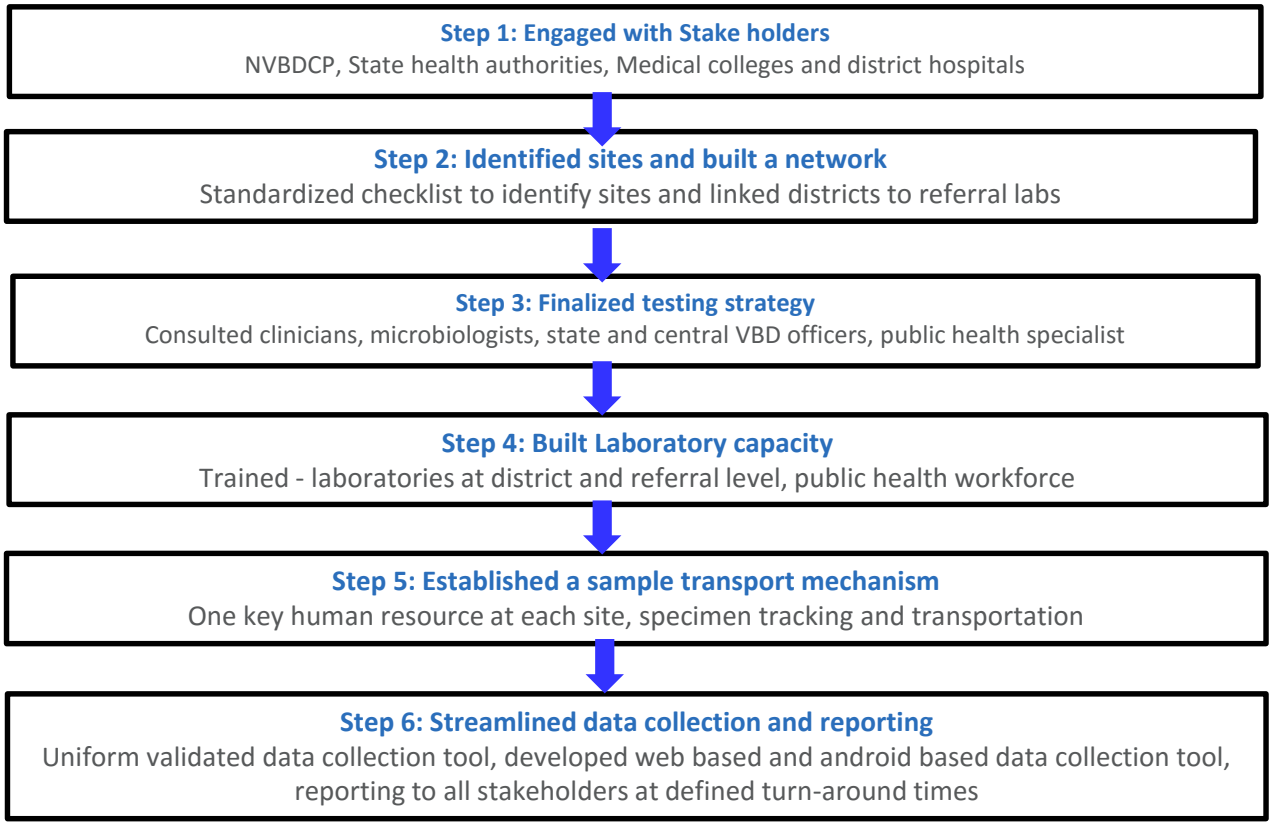
CLINICAL	Case Identification and Classification: •AES is a broad umbrella term that can encompass a wide range of diagnoses
LABORATORY	Lack of a Standard Testing Algorithm: •Routine district-level testing is primarily focused on JE •Lack of a standard laboratory algorithm to support diagnosis and identify treatable non-JE etiologies Laboratory Network with Robust Sample Referral System : •Strengthen existing district capacity and enhance linkages with referral level laboratories to support advanced diagnostic testing
EPIDEMIOLOGIC	Surveillance Data Flow •Enhance existing data reporting and analysis for decision making
ADMINISTRATIVE	**Multiple stakeholders** National program officers, state health authorities, district health officials, medical colleges, clinicians, nodal agencies.

Objectives of the study

1. **Work with state and national programs to establish a tiered network to support & strengthen laboratory based surveillance of JE/AES in India**
   - Strengthen district laboratory capacity for JE testing
   - Strengthen referral laboratory capacity for testing additional (non-JE) pathogens that may cause AES
   - Establish external quality assurance program with proficiency testing
   - Establish and enhance specimen transport and reporting of results

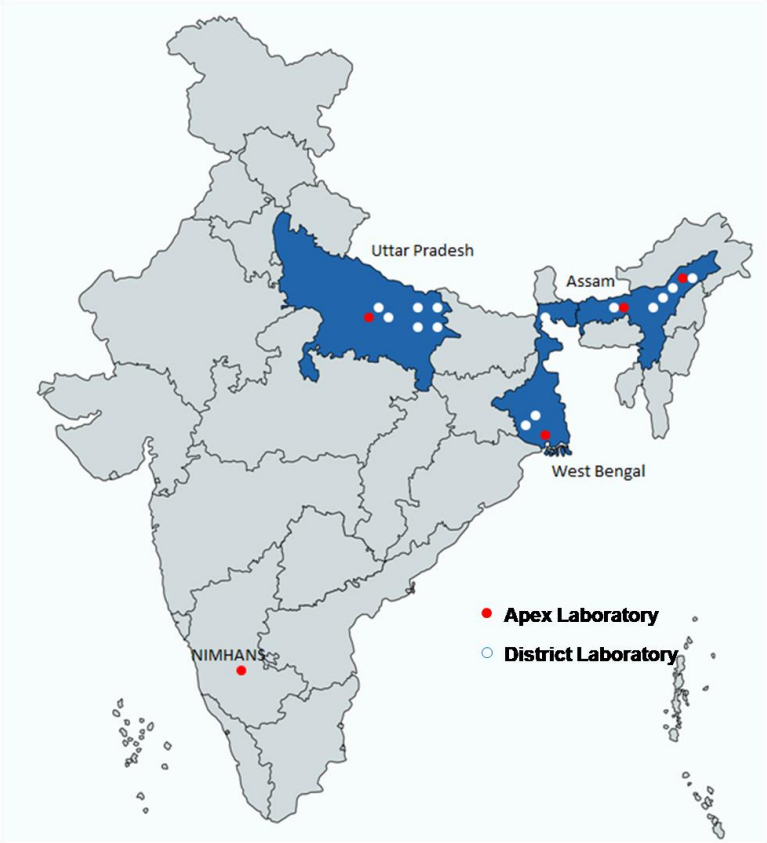
2. **Enhance the understanding of etiologies and epidemiology of AES in highly affected states**
   - Develop and use a standardized laboratory testing algorithm for JE & Non JE pathogens
   - Streamline data collection and reporting of results
     - Guide modification of routine surveillance
     - Develop appropriate public health and clinical intervention

AES Surveillance : What did we do?



BMJ

Project Sites, 2014 – 2017



State	Apex Laboratory	Districts
Uttar Pradesh	King George Medical University	Deoria* Kushinagar* Siddharth Nagar Maharajganj Sitapur* Lakhimpur Kheri*
Assam	Assam Medical College Guwahati Medical College	Dibrugarh* Jorhat Sibsagar Guwahati/Kamrup*
West Bengal	School of Tropical Medicine	Bankura Burdwan* Siliguri
Karnataka	NIMHANS	Bellary*

* Sites functional since 2014

Site selection performed in consultation with national and state NVBDCP offices

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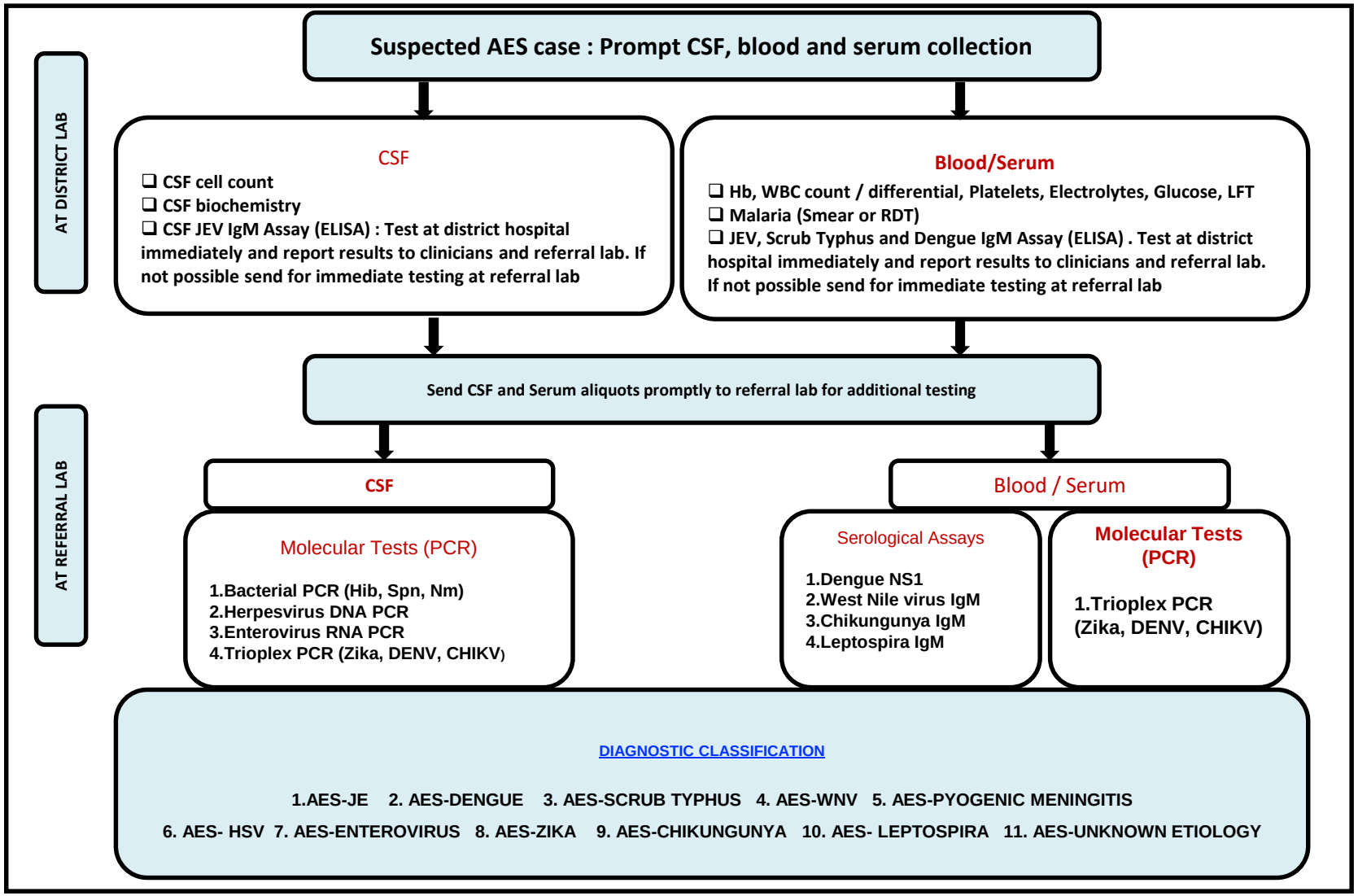
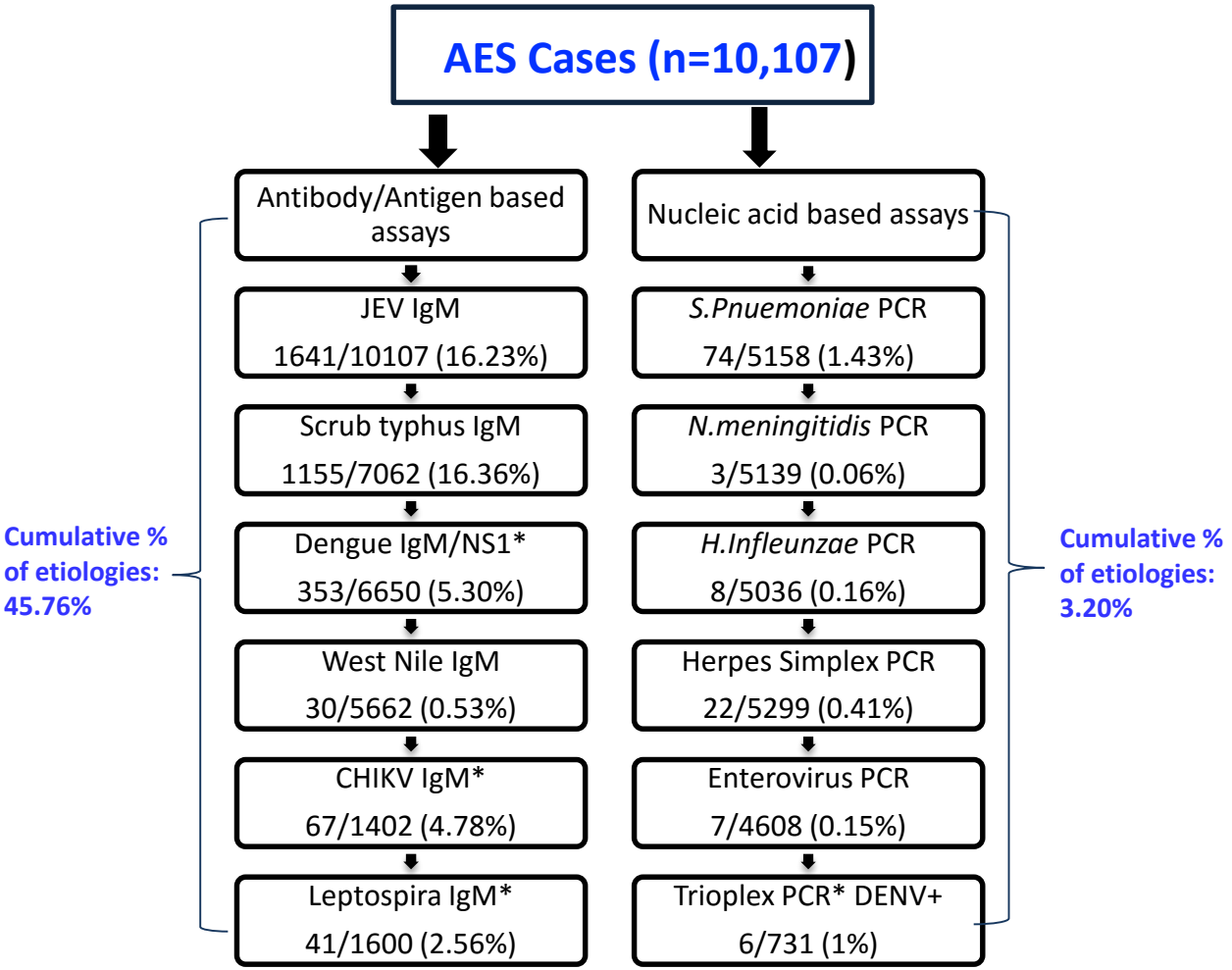
Standardized AES laboratory testing algorithm



Salient socio-demographic details of AES cases enrolled in the network over a four-year period (2014-17)

State	Assam	UP	West Bengal	Total
AES cases enrolled	5415	2797	1895	10107
Age range (in Years)	n=5409	n=2796	n=1652	n=9857
<15	2756 (51%)	2445 (87%)	979 (59%)	6180 (63%)
Gender	n=5415	n=2797	n=1705	n=9917
Male	3308 (61%)	1459 (52%)	967 (57%)	5734 (58%)
Specimen collected	Assam	UP	West Bengal	Total
Serum & CSF	2918 (54%)	2141 (77%)	875 (46%)	5934 (58%)
Serum	1629 (30%)	474 (17%)	394 (21%)	2497 (24%)
CSF	868 (16%)	182 (7%)	626 (33%)	1676 (17%)
Total	5415	2797	1895	10107
Mortality	605/4226 (14%)	80/1920 (4%)	263/1331 (20%)	948/7477 (13%)

Summary of AES Surveillance Network:
Jan 2014-Dec 2017



- ❖ 45,315 AES cases reported to NVBDCP in 2014 – 2017
- 31,092 AES cases from UP, Assam, WB, Karnataka (69% of total)
- 10,107 AES cases tested represents 33% of reported AES cases in these states

❖Overall the application of testing algorithm resulted in etiologic identification in 49% of cases

- JE, Scrub Typhus, Dengue account for almost 93% of these cases

JEV, Scrub Typhus and Dengue Diagnoses, 2014 – October 2017

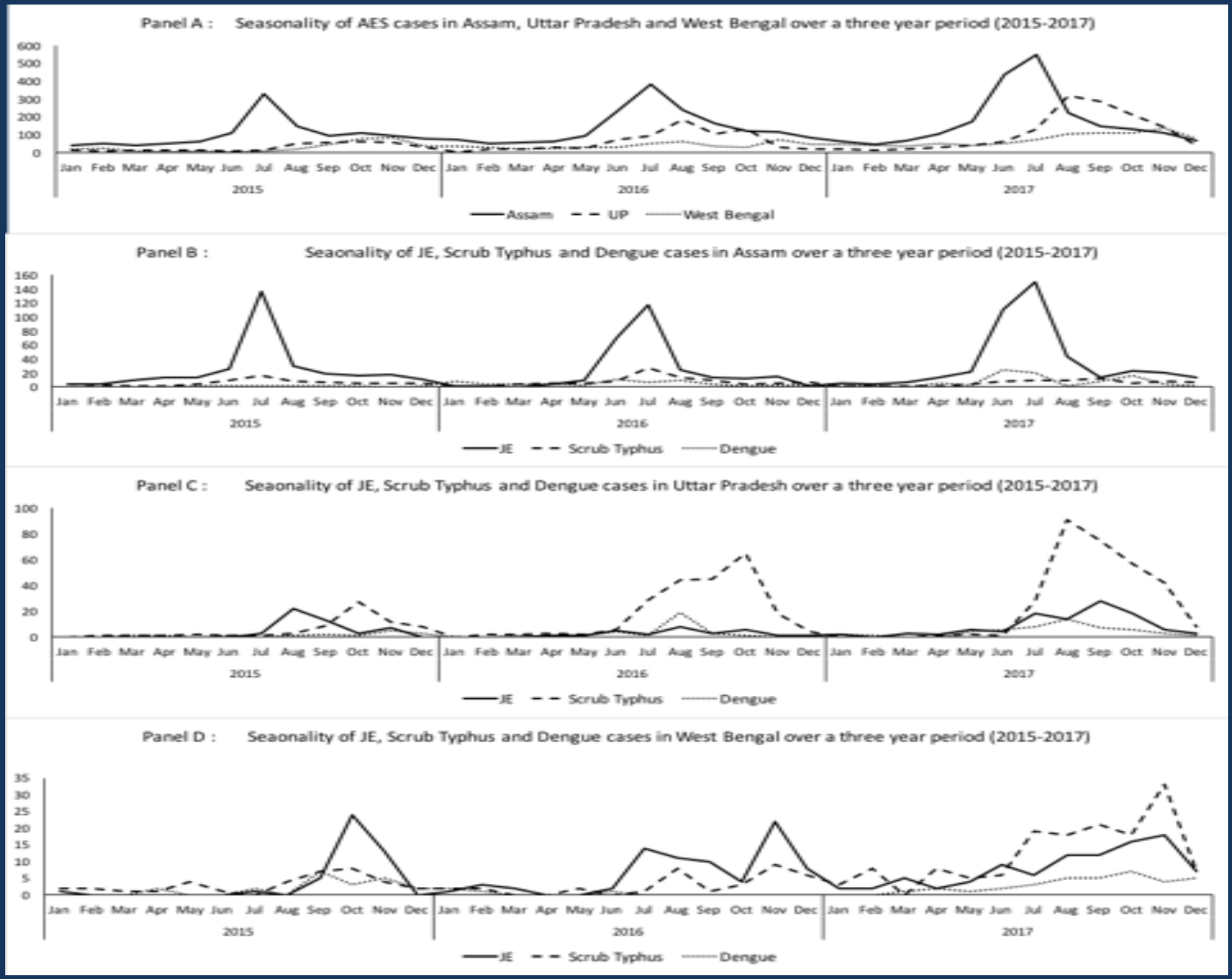
Year	JE Diagnostic Testing Results	Assam	West Bengal	Uttar Pradesh
2014	JE Diagnosis*	157/409 (38 %)	47/190 (25%)	56/396 (14%)
	Scrub typhus IgM+	22/162 (14%)	5/92 (5%)	191/403 (47%)
	Dengue IgM+	2/149 (1%)	2/78 (3%)	27/456 (6%)
2015	JE Diagnosis*	315/1210 (26%)	53/351 (15%)	63/343 (18%)
	Scrub typhus IgM+	71/509 (14%)	36/107 (34%)	127/465 (27%)
	Dengue IgM+	16/238 (7%)	27/144 (19%)	18/526 (3%)
2016	JE Diagnosis*	287/1672 (17%)	77/473 (16%)	77/742 (10%)
	Scrub typhus IgM+	93/1043 (9%)	34/100 (34%)	333/914 (36%)
	Dengue IgM+	68/1044 (7%)	5/108 (5%)	73/1010 (7%)
2017**	JE Diagnosis*	460/1826 (25%)	66/557 (12%)	215/898 (24%)
	Scrub typhus IgM+	50/1340 (4%)	97/298 (33%)	263/761 (35%)
	Dengue IgM+	55/821 (7%)	31/303 (10%)	104/867 (12%)

*JE Diagnosis: CSF JEV IgM+ OR Serum JEV IgM+

Among GHSA-NIMHANS Sites:

- ***Assam Sites:***
  - JE most common etiology
  - Scrub typhus less common
  - Dengue accounts for 10-15%
- ***West Bengal Sites:***
  - JE accounts for ~12% of AES
  - Scrub typhus: prevalence >20%
  - Dengue notable
- ***Uttar Pradesh Sites***
  - JE accounts for ≤ 10% AES
  - Scrub typhus prevalence >25%
  - Dengue: 4-8% of AES

Seasonality of AES in North India (2015-17)



Relative Risk factor study for Scrub typhus

- **Policy:**
  - Recognition of scrub typhus as an entity
  - Revision of National AES testing algorithm
  - Sustainability through NHM
- **Collateral spin-offs**
  - Zika surveillance system – GBS and AES
  - Scrub typhus risk factor study with ICMR, WHO, MCVR
  - AFI-AES combined surveillance with MCVR
  - Digital platform for data collection and reporting

Risk factors associated with scrub typhus, Gorakhpur and Deoria districts, Uttar Pradesh, 2017 (multivariate analysis)

Risk factor	Adjusted Odds Ratio (95% CI)	Adjusted Population attributable fraction (95% CI)
Location of house within/ adjoining field	1.59 (1.04 -2.43)	15.2 (3.5-25.5)
Went for defecation in the field in the last 2 weeks (vs toilet or around house)	2.20 (1.39-3.48)	14.4 (8.7-19.8)
Visited agriculture field in the last 2 weeks	1.66 (1.09-2.52)	9.2 (3.2-14.9)
Storage of firewood inside house/verandah	1.59 (1.05-2.41)	7.8 (2.1-13.2)
Playing in the field in the last 2 weeks (vs indoor or around house)	2.11 (1.12-3.97)	2.1 (0-6.2)
Fed cattle in the last 2 weeks	1.87 (1.08-3.26)	-5.0
Bathing in river/nullah	1.73 (0.80-3.79)	5.0(0-12.2)

(Adjusted for age)

?

Accepted for publication in ***Emerging Infections Diseases*** (Nov 2018)

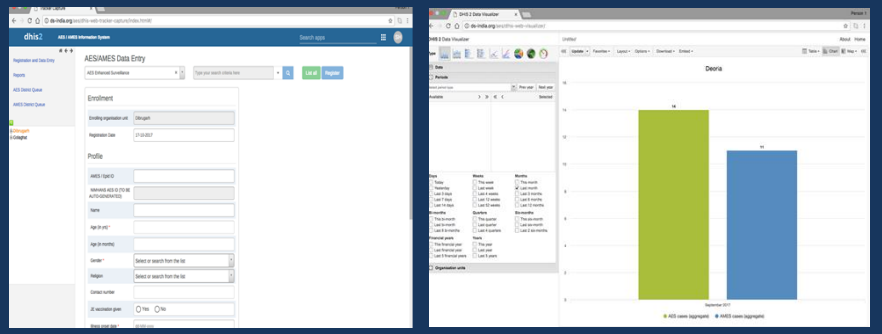
Geographic Distribution of Scrub Typhus

From: Scrub Typhus: The Geographic Distribution of Phenotypic and Genotypic Variants of Orientia tsutsugamushi
Clin Infect Dis. 2009;48(Supplement_3):S203-S230. doi:10.1086/596576

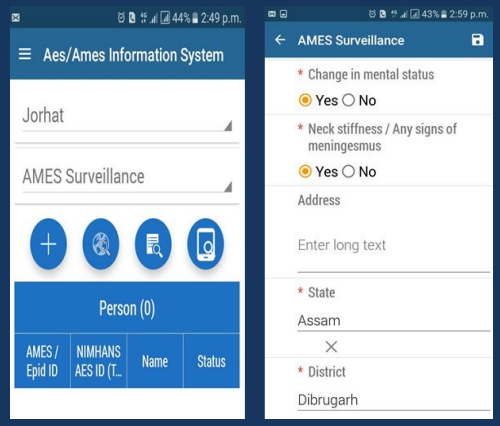
AES Surveillance Health Informatics Platform

- Inter-linked Web-based and Android App-based health informatics platforms developed for AES surveillance network
  - In collaboration with Health Information Systems (HISP) India
  - Utilizes District Health Information Systems 2 (DHIS2) platform, already in use by NVBDCP
- Real-time data entry, management, analytics, and reports
- SMS alerts sent to treating physicians and site coordinators if test result is positive

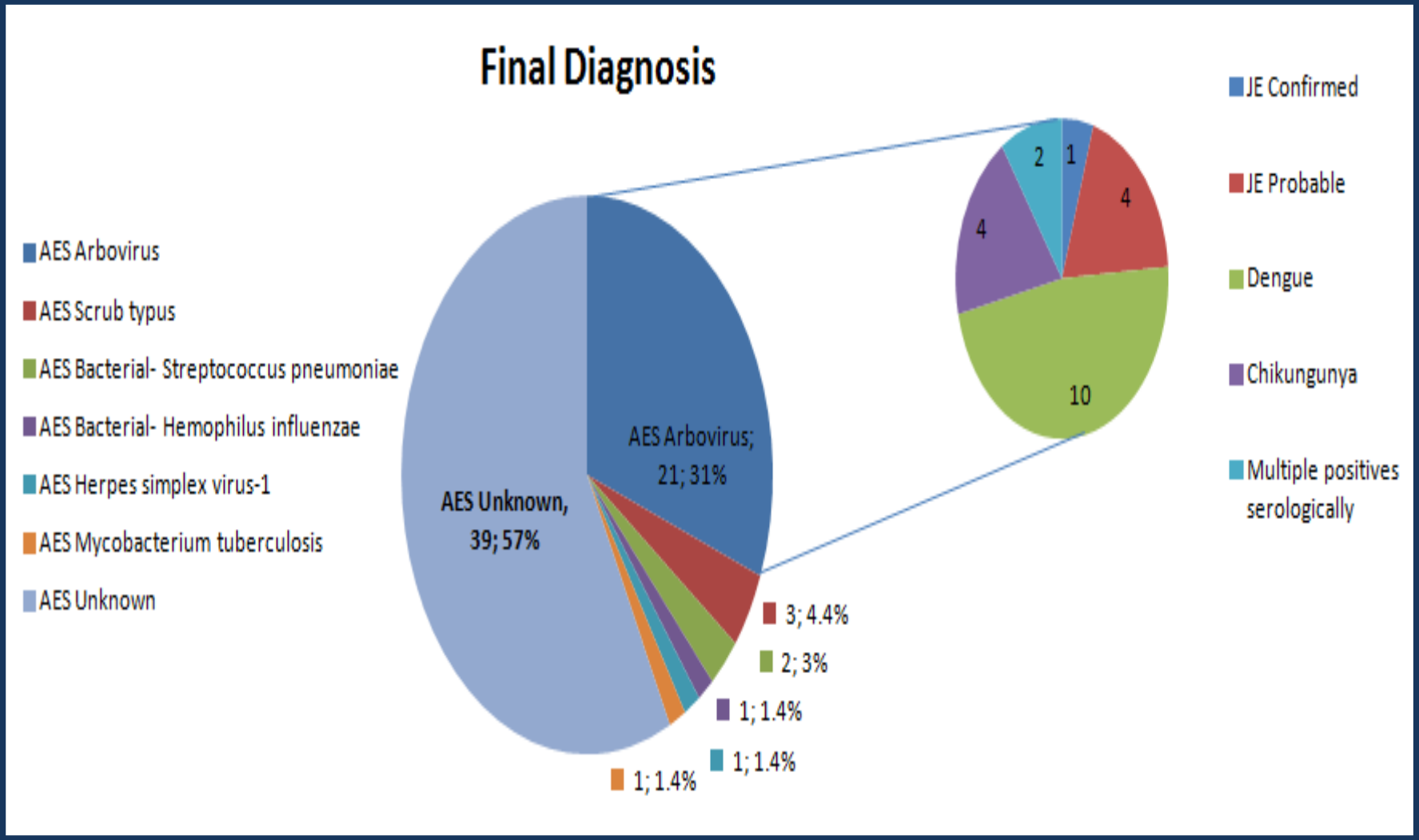
Web based DHIS2 Platform



Android App – DHIS2 Platform

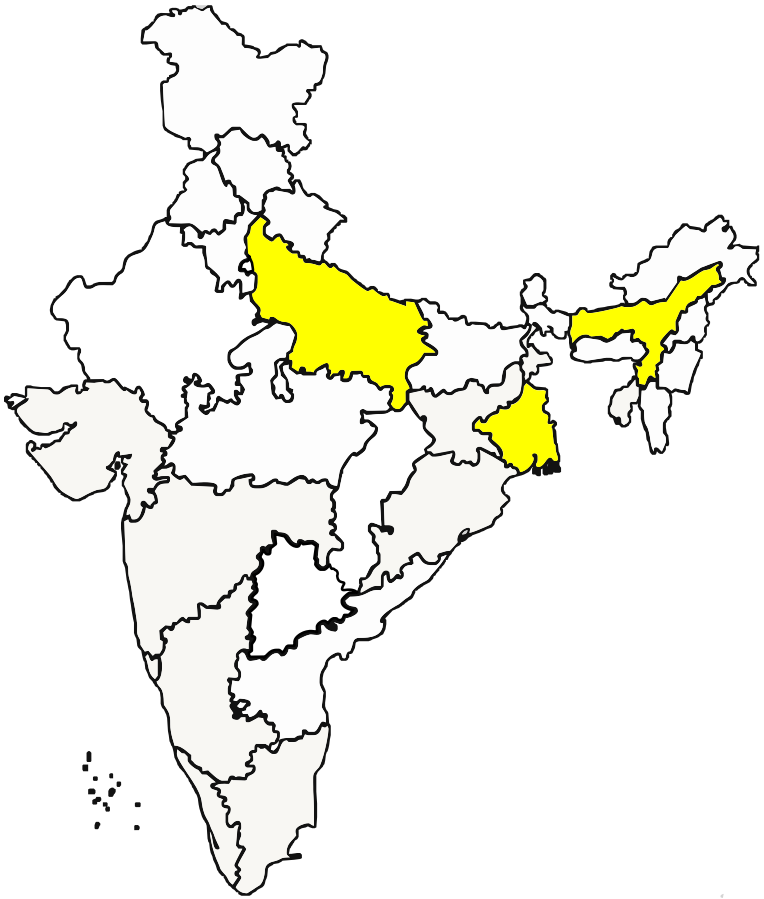


Etiology of Pediatric AES-Bangalore (n=108)



Real-time Sentinel Infectious Disease Surveillance in India, 2014 – 2016

States with Sentinel Infectious Disease Surveillance Sites



- Surveillance of 40, 000 patients admitted to district and sub-district hospitals with acute febrile illness and/or acute encephalitis syndrome
- Systematic laboratory testing resulted in etiologic diagnosis in 40%
- Top 7 pathogens identified:
  - Dengue
  - Influenza
  - Japanese Encephalitis
  - Kyasnur Forest Disease
  - Leptospirosis
  - Malaria
  - Scrub Typhus

AFI/AES overlapping surveillance: Study design

- Prospective case control design
- Initiated from1st August 2018- Ongoing until 31st Dec 2018
- Two sites were selected – One PHC at Rampur Karkhana and One District Hospital at Deoria town.
- Standard AFI and AES case definitions
- Serum samples at PHC tested using Rapid diagnostic tests and subsequently transported same day to District hospital laboratory for confirmation by ELISA. Throat swab, urine stool samples transported to MCVR, Manipal
- Testing strategies used were identical to AFI/AES surveillance carried out earlier by MCVR and NIMHANS respctively

Interim results

Etiology identified on PHC patients	AFI (n=311)	AFI with altered mental status/seizure	Total (n=329)
CHIK	5 (1.6%)	0	5 (1.5%)
DEN	27 (8.7%)	0	27 (8.2%)
DEN (IgM+NS1)	4 (1.3%)	0	4 (1.2%)
DEN IgM+CHIK	15 (4.8%)	0	15 (4.6%)
DEN IgM+LEPT	2 (0.6%)	0	2 (0.6%)
DEN IgM+LEPT+CHIK	1 (0.3%)	0	1 (0.3%)
DEN IgM+ST	3 (1%)	0	3 (0.9%)
DEN IgM+ST+CHIK	4 (1.3%)	0	4 (1.2%)
DEN NS1+ST	2 (0.6%)	0	2 (0.6%)
DEN NS1+ST+LEPT+CHIK	1 (0.3%)	0	1 (0.3%)
LEPT	11 (3.5%)	1 (5.6%)	12 (3.6%)
LEPT+CHIK	1 (0.3%)	0	1 (0.3%)
NS1	3 (1%)	1 (5.6%)	4 (1.2%)
ST	30 (9.6%)	1 (5.6%)	31 (9.4%)
ST+CHIK	1 (0.3%)	0	1 (0.3%)
ST+LEPT	2 (0.6%)	0	2 (0.6%)
Grand Total	112 (36%)	3 (16.7%)	115 (35%)

Etiology identified on District hospital patients	AFI (n=227)	AFI with altered mental status/seizures (n=266)	Total (n=493)
CHIK	2 (0.9%)	4 (1.5%)	6 (1.2%)
DEN	16 (7%)	15 (5.6%)	31 (6.3%)
DEN(IgM+NS1)+LEP	0	1 (0.4%)	1 (0.2%)
DEN(IgM+NS1)+ST+CHIK	2 (0.9%)	0	2 (0.4%)
DEN(IgM+NS1)	2 (0.9%)	0	2 (0.4%)
DEN(IgM+NS1)+WNV	1 (0.4%)	0	1 (0.2%)
DEN+CHIK	8 (3.5%)	5 (1.9%)	13 (2.6%)
DEN+ST	3 (1.3%)	9 (3.4%)	12 (2.4%)
DEN+ST+CHIK	4 (1.8%)	5 (1.9%)	9 (1.8%)
LEP	2 (0.9%)	2 (0.8%)	4 (0.8%)
LEP+CHIK	1 (0.4%)	0	1 (0.2%)
LEP+WNV+CHIK	1 (0.4%)	0	1 (0.2%)
NS1	0	4 (1.5%)	4 (0.8%)
NS1+ST	2 (0.9%)	4 (1.5%)	6 (1.2%)
NS1+ST+LEP	0	1 (0.4%)	1 (0.2%)
ST	57 (25.1%)	89 (33.5%)	146 (29.6%)
ST+CHIK	6 (2.6%)	5 (1.9%)	11 (2.2%)
ST+LEP	1 (0.4%)	1 (0.4%)	2 (0.4%)
WNV+CHIK	2 (0.9%)	0	2 (0.4%)
Total	110 (48.5%)	145 (54.5%)	255 (51.7%)

Interim summary of overlapping surveillance

- The etiological pattern of AFI between the PHC and district hospital were quite distinct
- District hospital at Deoria town has a large catchment area for patients as it caters to several other PHCs (16)& CHCs (8)
- Etiological agents were identified in 35% of AFI cases at Rampur Karkhana PHC (Influenza results are pending). Amongst those with an etiology Scrub typhus (9.6%), Dengue (8.7%), Chikungunya(1.6%) and leptospirosis(3.5%) accounted for 65% of cases
- Etiological agents were identified in 48% of AFI cases at Deoria district hospital (Influenza results are pending). Amongst those with an etiology Scrub typhus (25%), Dengue (7%), Chikungunya (1%) and leptospirosis(1%) accounted for 70% of cases.
- Etiological agents were identified in 54% 0f AES cases enrolled at Deoria district hospital. Amongst those with an etiology, Scrub typhus (33.5%), Dengue (5.5%), Chikungunya (1.5%) and Leptospirosis (1%) accounted for 75% of all cases.
- The number of AES cases reported from Rampur Karkhana in 2018 were only 11/266 (4%) cases. In contrast the number of AES cases reported form the same block between 2015&2016 were totally 74/859(9%). This clearly indicates that there is 50% reduction in AES because of initiating AFI surveillance at this PHC. Further, all the 11 cases 2018 did not report with fever to the PHC before presenting as AES directly to Deoria hospital

Nipah virus: Anatomy of the 2018 outbreak

- May 17th, 2 A.M: 28 year/M,

architect Mohd Salih rushed to Kozhikode's Baby Memorial Hospital

- High grade fever, vomiting, altered

sensorium (agitation)

- Heart rate:180/ minute; hypertensive
- ↓ reflexes.

<u>Differential diagnosis considered</u>

- R/O Japanese encephalitis (typically doesn't affect more than one person in a household);

His younger brother Mohd. Sabith died about 12 days ago after showing similar symptoms (patient zero),

Rabies, Toxin mediated (R/O)

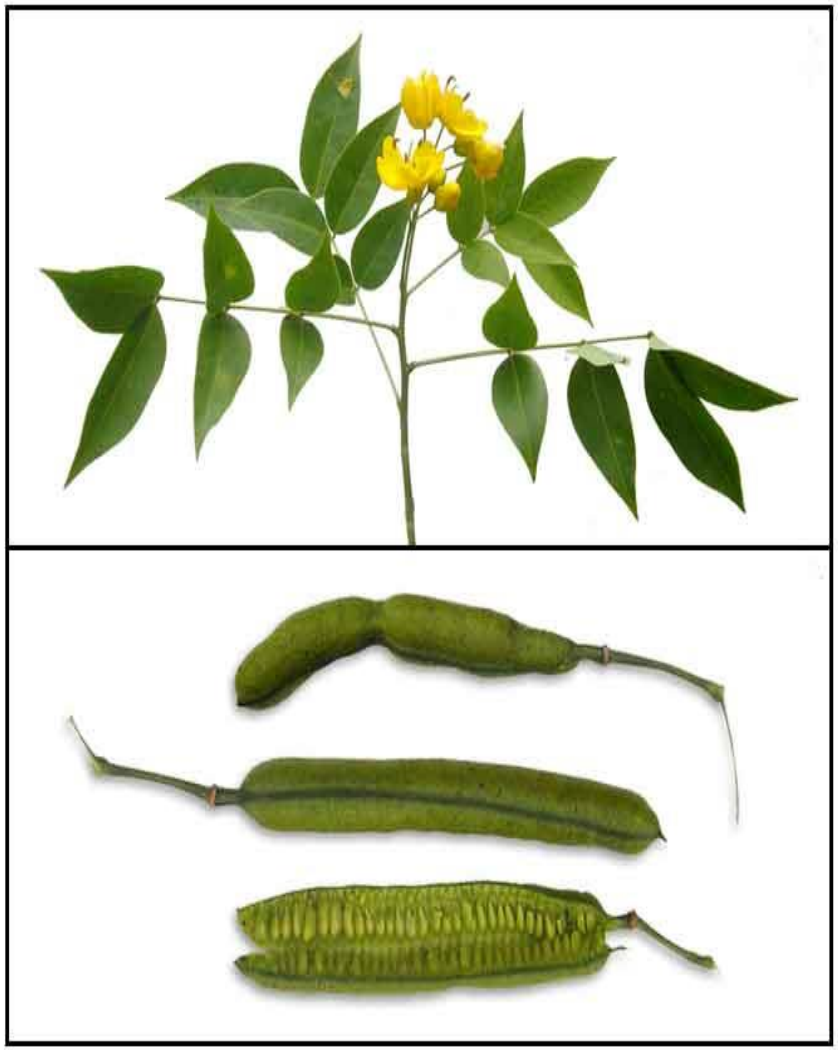
- Father and aunt, too, contracted the infection and later succumbed

Non-Infectious causes of AES identified in India

- Toxins
- Metabolic encephalopathy
- Autoimmune encephalitis

'Saharanpur' Encephalitis (Western UP)

- Outbreaks of unexplained 'encephalitis' in children every year- 2 decades; Very high mortality (70-80%)
- Not encephalitis, but a multi-system disease affecting liver, muscle and brain
- Re-named "acute hepatomyoencephalopathy (HME) syndrome" caused by phytotoxins.
- Source of toxicity was found to be to the consumption of beans of a ubiquitous weed *Cassia occidentalis* by young children of poor families
- Cases occurred only in September-December every year coinciding with the poding season of this annual plant.
- 2008-2012 Shaharanpur, UP, 2017 Malkangiri, Orissa



AES in Muzaffarpur, Bihar
What was known from 2014 study

- Annual seasonal outbreaks during the months of April– July, 2 decades
- Affects hundreds of children; 40–60% mortality
- ?JE ? Heat stroke ?Nipah ?WNV
- Coincided spatially and temporally with lychee cultivation & harvest
- **Typical Clinical features:** sudden onset without prodromal phase, inconsistent presence of fever, brain oedema, acellular CSF and hypoglycaemia
- Sparing of children below 2
- Children well until evening, but early next morning found seriously ill with brain function derangement and seizures.
- Consistent association- **Malnourished children**
- **Toxic encephalopathy-** Lychee contains toxin MCPG- causes hypoglycemia
- Well-nourished children not affected since their glycogen/glucose store in the liver is sufficient to maintain normal glucose levels
- Similar outbreak in litchi growing areas in Malda District (West Bengal)-June 2014

Lancet Glob Health 2017;
5: e458–66

Articles

Association of acute toxic encephalopathy with litchi consumption in an outbreak in Muzaffarpur, India, 2014: a case-control study

Aakash Shrivastava, Anil Kumar, Jerry D Thomas, Kayla F Laserson, Gyan Bhushan, Melissa D Carter, Mala Chhabra, Veena Mittal, Shashi Khare, James J Sejvar, Mayank Dwivedi, Samantha L Isenberg, Rudolph Johnson, James L Pirkle, Jon D Sharer, Patricia L Hall, Rajesh Yadav, Anoop Velayudhan, Mohan Papanna, Pankaj Singh, D Somashekar, Arghya Pradhan, Kapil Goel, Rajesh Pandey, Mohan Kumar, Satish Kumar, Amit Chakrabarti, P Sivaperumal, A Ramesh Kumar, Joshua G Schier, Arthur Chang, Leigh Ann Graham, Thomas P Mathews, Darryl Johnson, Liza Valentin, Kathleen L Caldwell, Jeffery M Jarrett, Leslie A Harden, Gary R Takeoka, Suxiang Tong, Krista Queen, Clinton Paden, Anne Whitney, Dana L Haberling, Ram Singh, Ravi Shankar Singh, Kenneth C Earhart, A C Dhariwal, L S Chauhan, S Venkatesh, Padmini Srikantiah

Summary

Background Outbreaks of unexplained illness frequently remain under-investigated. In India, outbreaks of an acute neurological illness with high mortality among children occur annually in Muzaffarpur, the country's largest litchi cultivation region. In 2014, we aimed to investigate the cause and risk factors for this illness.

Methods In this hospital-based surveillance and nested age-matched case-control study, we did laboratory investigations to assess potential infectious and non-infectious causes of this acute neurological illness. Cases were children aged 15 years or younger who were admitted to two hospitals in Muzaffarpur with new-onset seizures or altered sensorium. Age-matched controls were residents of Muzaffarpur who were admitted to the same two hospitals for a non-neurologic illness within seven days of the date of admission of the case. Clinical specimens (blood, cerebrospinal fluid, and urine) and environmental specimens (litchis) were tested for evidence of infectious pathogens, pesticides, toxic metals, and other non-infectious causes, including presence of hypoglycin A or methylenecyclopropylglycine (MCPG), naturally-occurring fruit-based toxins that cause hypoglycaemia and metabolic derangement. Matched and unmatched (controlling for age) bivariate analyses were done and risk factors for illness were expressed as matched odds ratios and odds ratios (unmatched analyses).

Findings Between May 26, and July 17, 2014, 390 patients meeting the case definition were admitted to the two referral hospitals in Muzaffarpur, of whom 122 (31%) died. On admission, 204 (62%) of 327 had blood glucose concentration of 70 mg/dL or less. 104 cases were compared with 104 age-matched hospital controls. Litchi consumption (matched odds ratio [mOR] 9·6 [95% CI 3·6 – 24]) and absence of an evening meal (2·2 [1·2–4·3]) in the 24 h preceding illness onset were associated with illness. The absence of an evening meal significantly modified the effect of eating litchis on illness (odds ratio [OR] 7·8 [95% CI 3·3–18·8], without evening meal; OR 3·6 [1·1–11·1] with an evening meal). Tests for infectious agents and pesticides were negative. Metabolites of hypoglycin A, MCPG, or both were detected in 48 [66%] of 73 urine specimens from case-patients and none from 15 controls; 72 (90%) of 80 case-patient specimens had abnormal plasma acylcarnitine profiles, consistent with severe disruption of fatty acid metabolism. In 36 litchi arils tested from Muzaffarpur, hypoglycin A concentrations ranged from 12·4 µg/g to 152·0 µg/g and MCPG ranged from 44·9 µg/g to 220·0 µg/g.

Interpretation Our investigation suggests an outbreak of acute encephalopathy in Muzaffarpur associated with both hypoglycin A and MCPG toxicity. To prevent illness and reduce mortality in the region, we recommended minimising litchi consumption, ensuring receipt of an evening meal and implementing rapid glucose correction for suspected illness. A comprehensive investigative approach in Muzaffarpur led to timely public health recommendations, underscoring the importance of using systematic methods in other unexplained illness outbreaks.

Funding US Centers for Disease Control and Prevention.

Introduction

In India, seasonal outbreaks of an acute unexplained neurological illness have been reported since 1995 from Muzaffarpur, Bihar, the largest litchi (lychee) fruit cultivation region in the country.[1] These recurring outbreaks begin in mid-May and peak in June, coinciding with the month-long litchi harvesting season. Children from poor socioeconomic backgrounds in rural Muzaffarpur comprise most of those affected. Illness is characterised by acute seizures and changed mental

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Current status of AES outbreak

	SKMCH	KDKMH	Tota
New admissions on 20 June	26	5	31
Deaths on 26 June	2	0	2
Total AES cases till date	398	154	552
Total deaths	98	20	118 (21.4%

Cases of AES by date of hospitalization, Muzaffarpur area, Bihar, 2019

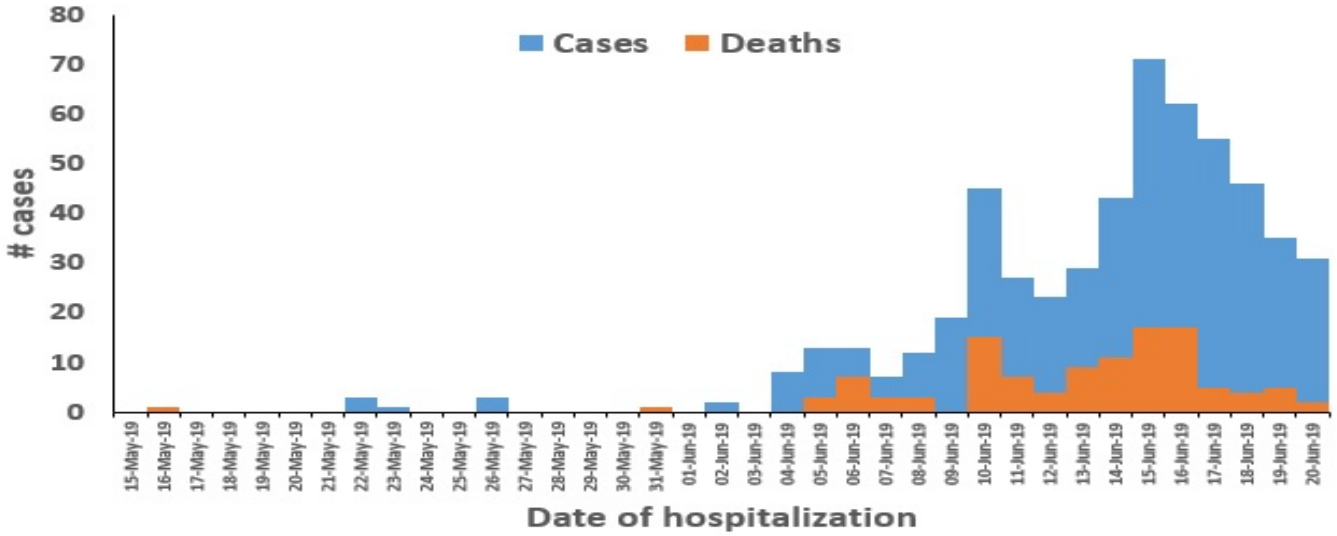
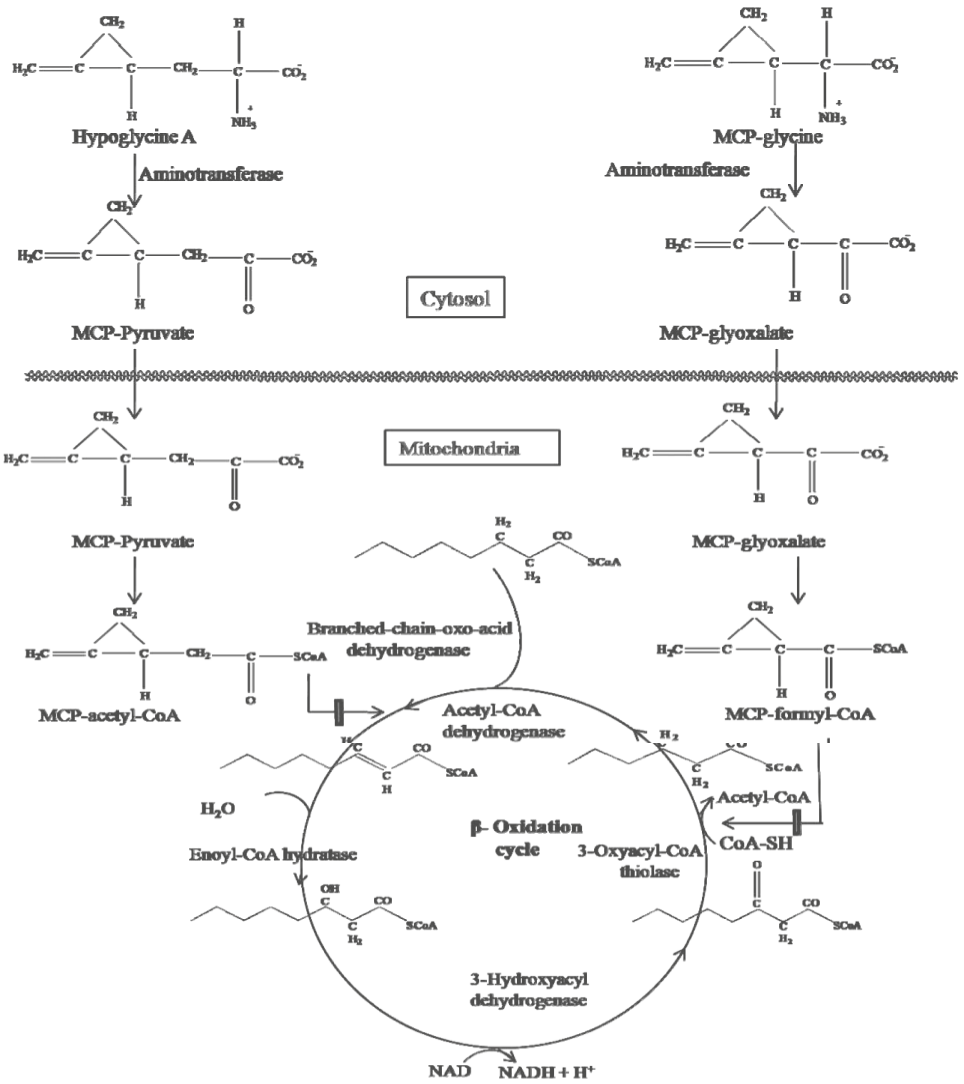


Figure 1. Conversion of MCPG and hypoglycine into active metabolites and their sites of inhibition of oxidation16.



Clinical Findings – No Inflammation

CLINICAL CHARACTERISTICS	N=390	
Mortality	31%	(121/390)
Temperature on admission <99.5F	61%	(219/359)
Time of illness onset between 3am – 8am	66%	(257/390)
Blood glucose on presentation <70 mg/dL (hypoglycaemia)	62%	(204/327)
CSF examination with WBC < 5 cells/mm^3	84%	(52/62)
Brain MRI with no focal lesions	100%	(16/16)
EEG with generalized encephalopathy	100%	(30/30)

Case Control Study -- Matched Bivariate Analysis

KEY RISK FACTORS	CASES (N=104)		CONTROLS (N=208)		mOR (95% CI)	
Ate litchi*	65%	(67/103)	48%	(98/204)	2.1	(1.2 – 3.5)
Ate rotten litchi*	26%	(23/88)	15%	(19/130)	2.4	(1.0 – 5.5)
Visited fruit orchard*	52%	(52/100)	32%	(62/195)	2.9	(1.6 – 5.1)
Parent visited fruit orchard*	31%	(29/95)	20%	(39/198)	1.8	(1.0 – 3.1)
Last meal before 6pm*	55%	(54/98)	36%	(63/176)	2.0	(1.2 – 3.2)
Higher SES**	8%	(8/102)	16%	(33/207)	0.4	(0.2 – 0.9)
Routinely wash vegetables and fruits	32%	(32/99)	56%	(102/183)	0.32	(0.2 – 0.6)

** 24 hours before illness*

*** SES : Socio -Economic Status*

Effect of Eating Litchi Modified by Absence of Evening Meal

Last meal BEFORE 6pm

Exposure	mOR (95% CI)	
Ate litchis**	9.8	(0.6 – 159.6)

Last meal AFTER 6pm

Exposure	mOR (95% CI)	
Ate litchis**	0.3	(0.1 – 1.3)

* Controlling for SES and routinely washing vegetables and fruits
** 24 hours before illness

Muzaffarpur outbreak illness is an acute hypoglycemic encephalopathy due to toxicity from MCPG/Hypoglycin in litchis exacerbated by the absence of eating an evening meal

Investigations carried out in the Metabolic Laboratory, NIMHANS, Bengaluru

Free carnitine (C0) and a **panel of 30 acylcarnitines** (C2-C18) by **Tandem Mass Spectrometry**

Blood samples presumably collected before treatment

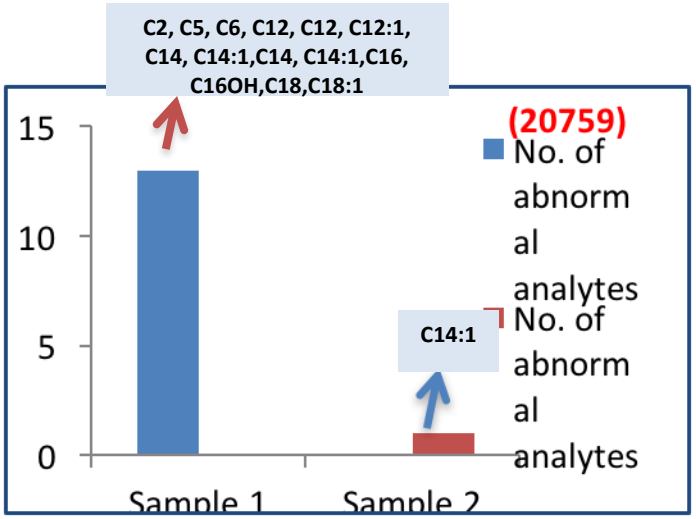
1. Plasma samples

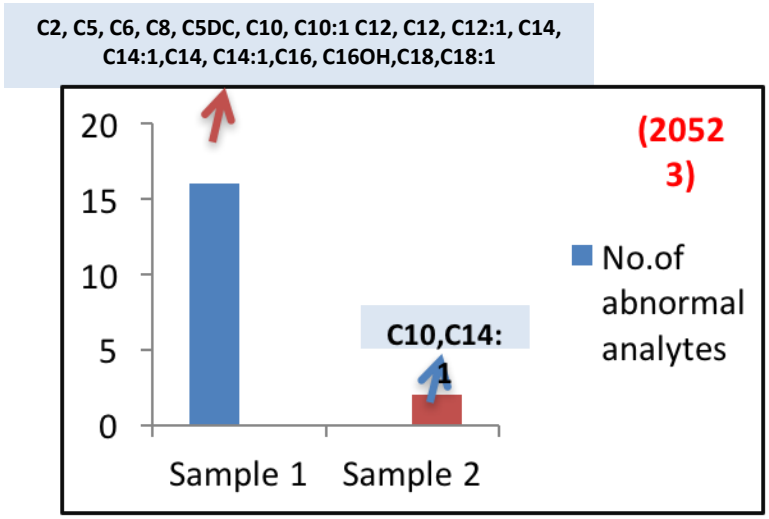
No of samples tested :	33
No of cases with abnormalities :	**25**
	(75.75%)

Types of abnormalities observed:

Decreased free carnitine:	**8**
cases	
Decreased free carnitine with elevated acylcarnitnes:	**8**
cases	
Elevated acylcarnitines (short, medium & long-chain) :	**9**
cases	

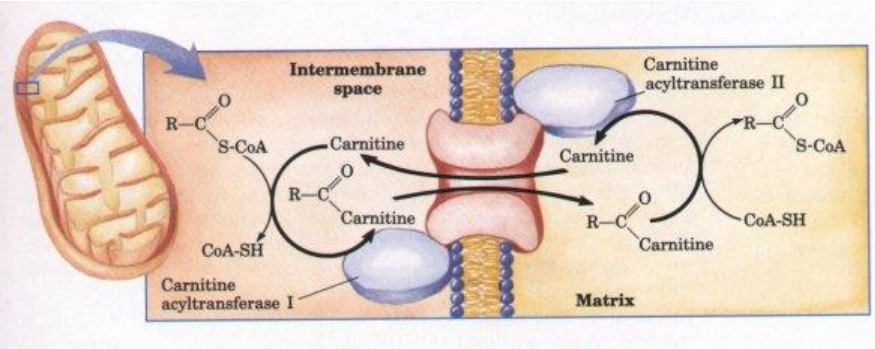
Blood acylcarnitines in samples before & after treatment





Carnitine

Quaternary amine essential for **transfer of long-chain fatty acids across the inner mitochondrial membrane** for subsequent β-oxidation



Causes of low plasma free carnitine

1. Primary carnitine deficiency

Deficiency in carnitine transporter (OCTN2)

2. **Secondary carnitine deficiency**

i) Loss of carnitine in the urine

Organic acids in blood: mono/dicarboxylic acids, methylenecyclopropylformyl Co-A(MCPF-Co-A)

Medication: valproic acid, pivalic acid, *etc*

Fanconi syndrome

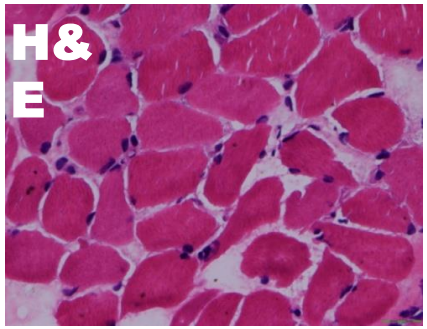
Toxins-MCPG

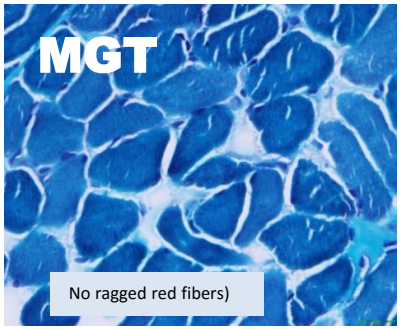
ii) Severe undernutrition

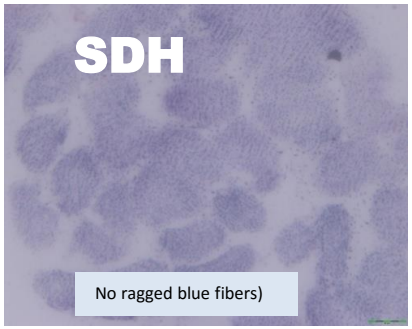
Anuska Kumari 7/F; Reg No. 20023

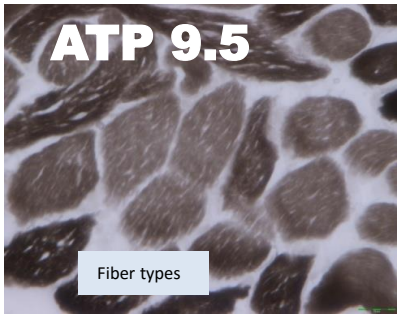
Ref by: Dr. Arun Singh, Professor Neonatology, National Advisor, RBSK MoHFW, Govt. of India
NIMHANS Ref: Npath No. X-3722/19 ; EM No. 187/19

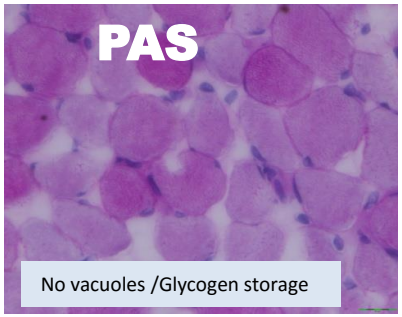
Histochemical stains on skeletal muscle











Histochemical stains shows mild fiber size variation
No evidence of mitochondrial pathology or storage material(glycogen, lipid)

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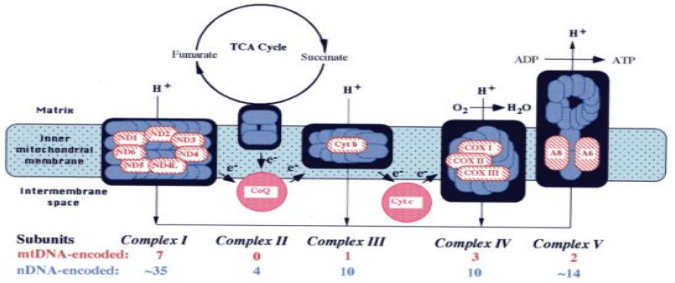
Respiratory chain enzyme assay on skeletal muscle

Test name	Result	% of control mean	Reference range	Units
Complex I	**0.08**	**27.89**	0.107-0.499 mean= 0.30	µmols DCIP reduced.min^{-1} mg protein^{-1}.unit citrate synthase^{-1}
Complex II	0.32	77.03	0.227-0.649 mean=0.42	µmols DCIP reduced.min^{-1} mg protein^{-1}.unit citrate synthase^{-1}
Complex III	0.73	163.39	0.161-0.609 mean=0.45	µmols Cytochrome C reduced.min^{-1} mg protein^{-1}.unit citrate synthase^{-1}
Complex IV	0.71	69.51	0.264-1.78 mean=1.02	µmols Cytochrome C oxidised.min^{-1} mg protein^{-1}.unit citrate synthase^{-1}

Conclusion : The respiratory chain activity of Complex I is ~30 %



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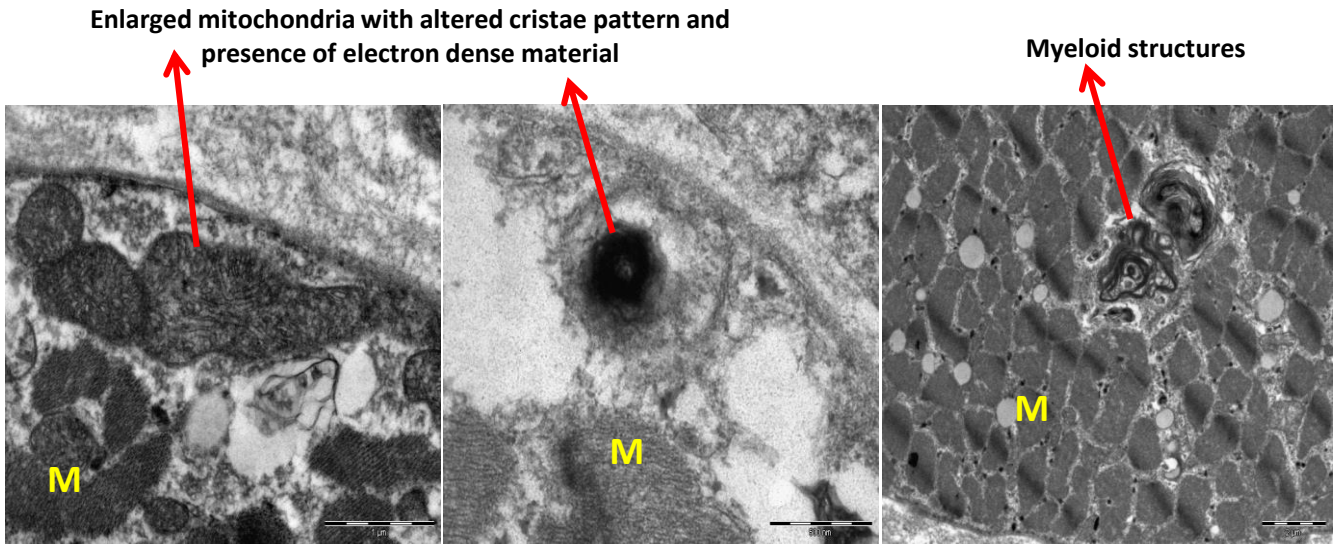
Electron micrographs of skeletal muscle

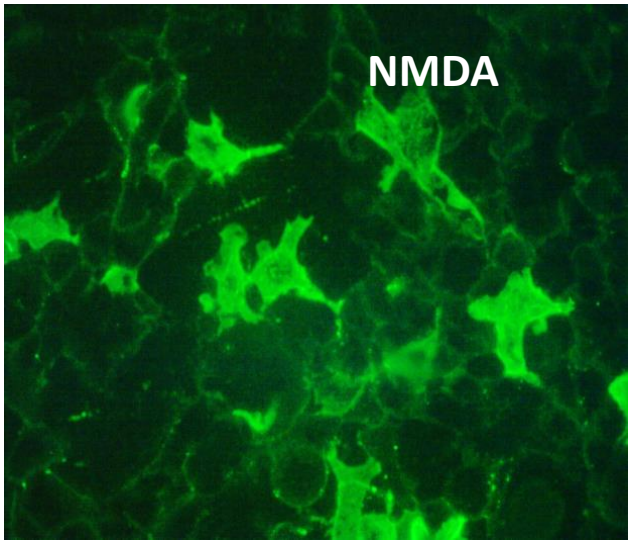


Ultrastructurally, skeletal muscle tissue shows a few enlarged mitochondria with altered cristae pattern and presence of electron dense material, presence of myeloid structures and distortion of myofilamentous pattern in a few fibers

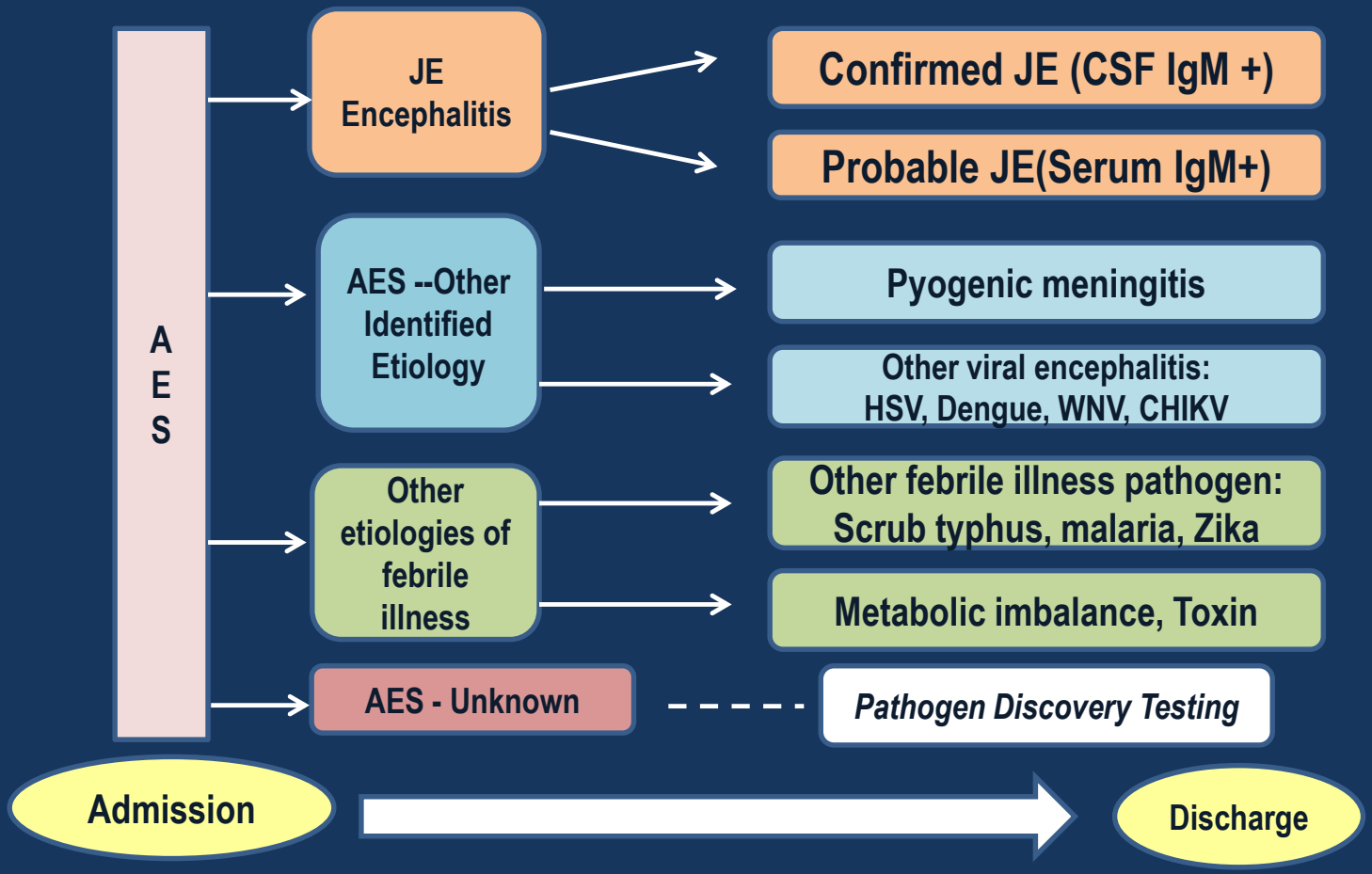
Neuromusular Lab
(Aug 2014 – Dec 2017)

Autoimmune encephalitis mosaic -332/2778 (11.95%) positive

- NMDA -251 (75.6%)
- LGI -25(7.5%),
- CASPR -27(8.1%),
- GABA -5(1.5%),
- GAD -24 (7.2%)



AES: From Admission to Discharge



Time to revisit the nomenclature and use of the term AES?

OVERALL SUMMARY

Changing Scenario of AES in India

Emergence of Pathogen in a New Geographic Area	• JE, DENGUE, Chikungunya
Emergence / Recognition of New Pathogen	• NIPAH, • SCRUB TYPHUS
Changes in Health Care	• "Opportunistic" encephalitides in immunosuppressed • JC/CMV/HSV/HHV-6
Recognition of "new" etiologies of encephalitis	• Anti-synaptic receptor antibody mediated encephalitis • Toxin mediated encephalopathies

- The epidemiology of AES in India is changing
- Etiological diagnosis of AES is best achieved using standard testing algorithms
- Identification of treatable causes of AES should get preference in the algorithm
- AES is only an admission diagnosis and it cannot be a discharge diagnosis
- Strengthening laboratory networks and establishing robust sample referral mechanisms are essential for tackling outbreaks
- Preventive strategies need to be evidence based.

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Flora and fauna of NIMHANS campus